Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1 and 27-36 are pending in the application, with claim 1 being the independent claim. Support for new claims 27-36 can be found throughout the specification and in original claims 2-11. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Description of the Invention

The invention features a method for expressing an exogenous gene in a mammalian cell by introducing into a mammal comprising the cell a baculovirus, the genome of which comprises the exogenous gene.

Rejections Under 35 U.S.C. § 112

Claim 1 was rejected for alleged lack of enablement. This rejection is respectfully traversed.

The Invention is Not Limited to Treatment of Liver Diseases

The Office Action states that "the only context in which the claimed method is presented in the specification is in the context of therapeutic delivery to treat liver diseases. The specification does not provide any evidence ... of Applicants having contemplated any non-therapeutic in vivo use, or any other therapeutic use for non-liver diseases, such as colon or breast cancer." Applicant respectfully submits that this narrow interpretation of the specification and the claimed invention is unfounded.

Nothing in the specification suggests that the invention is limited to treatment of liver diseases. While such treatment methods certainly are encompassed by the claims, the specification clearly states that the disclosed methods are more general. As stated at page 10, lines 15-21, of the specification, "other cells which can be infected by a baculovirus, including cells of tissues and organs, can easily be identified.... Nearly all mammalian cells are potential targets of AcMNPV and other baculoviruses...." Additionally, the specification states that, "[i]n various embodiments, the mammal is a human, and the cell is a hepatocyte or a cell having an ASGP-R" [emphasis added]. Specification, pg. 3, lines 28-29. As asserted in the specification, the invention can be used in methods for treating a variety of disorders that are not 'liver diseases," including: (i) insulin-dependent diabetes, (ii) Gaucher's disease, which affects multiple tissues, including brain; and (iii) Menkes disease, which affects multiple tissues, including the central nervous system. Specification, pg. 12, line 20, through pg. 13, line 30. The specification also discloses the use of baculoviruses to express a gene, such as cytosine deaminase, to alter the activity of a drug or prodrug, such as 5-fluorocytosine. Specification, pg. 14, lines 17-21. At the time the present application was filed, cytosine

deaminase and 5-fluorocytosine were known to be applicable to methods of treating cancers such as colorectal cancer and breast cancer (see, e.g., Harris, *Gene Therapy 1*:170-175 (1994) and Huber, *Proc. Natl. Acad. Sci. USA 91*:8302-8306 (1994), enclosed).

Conventional principles of claim differentiation also indicate that Applicant contemplated the use of cells other than liver cells in the methods of the invention. While original claim 1 was not limited to particular cell types, original claim 10, which was dependent upon claim 1, was limited to hepatocytes. Similarly, original claim 21 was not limited to particular cell types, whereas dependent claim 23 was limited to hepatocytes. Nothing in the pending claim 1 limits the claim to methods involving hepatocytes, and the Examiner is not at liberty to read such a limitation into the claim. Thus, the Examiner has erred in concluding that claim 1 is limited to "a method for therapeutic delivery of virus vectors for liver disease by *in vivo* or *ex vivo* gene transfer."

The Specification Provides an Enabling Disclosure

The Office Action states that "the specification provides no guidance or evidence teaching the use of the claimed baculoviral vectors to infect non-liver cells." Office Action at 3. This conclusion is unfounded. As is stated at page 10, lines 10-21, of the specification, the methods described therein are applicable both to hepatocytes and to other cell types. The applicability of such a method to non-liver cells is evidenced by the Declaration of Frederick Boyce, filed October 8, 1997, which demonstrates use of the disclosed methods to achieve baculovirus-mediated exogenous gene expression in 15 of 19 mammalian cell types, such as kidney, skeletal muscle, skin, uterus, glia, spleen,

stomach, pancreas, neurons, and fibroblasts. The applicability of the disclosed and claimed method to non-liver cells also is evidenced by the Declaration of James Barsoum, filed June 17, 1998, which demonstrates use of the disclosed methods to achieve baculovirus-mediated exogenous gene expression in human colon and breast cells. Furthermore, Applicant notes that, although the specification does not contain working examples of baculovirus-mediated gene expression in non-hepatic cells, "compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether an example is disclosed." MPEP 2164.02. Thus, the rejection on the belief that the specification does not provide "evidence teaching the use of the claimed baculoviral vectors to infect non-liver cells" is misplaced. MPEP 2164.02

The Office Action Fails to Establish a Prima Facie Rejection for Lack of Enablement

The Office Action states that "there is insufficient guidance concerning specific promoters, routes of delivery, dosage amounts ... frequencies of administration, expression levels, or any combination of these parameters for achieving a therapeutic benefit in mammals." This interpretation of the specification is simply in error. The specification does, in fact, disclose specific promoters, routes of delivery, dosage amounts, and other guidance necessary to obtain expression and therapeutic benefit in mammals (see, e.g., pg. 15, line 11, through pg. 16, line 16, of the specification). Thus, the information that the Office Action alleges is missing is, in fact, contained in the specification. If it is the Examiner's contention that still additional information is absent from the specification, the Examiner must "specifically identify what information is missing and why one skilled in the art could not supply the information without undue

experimentation." MPEP 2164.04; MPEP 2164.06(a). The Office Action fails to satisfy this requirement. Given the guidance provided in the specification, a person of ordinary skill in the art would be able to administer the disclosed recombinant baculovirus to a mammal in a method of obtaining exogenous gene expression in the mammal without undue experimentation.

As stated above, the fact that the specification provides an enabling disclosure is evidenced by the Declarations of Drs. James Barsoum and Frederick M. Boyce, filed on June 17, 1998 and October 8, 1997, respectively. These Declarations provide numerous examples demonstrating that exogenous gene expression was obtained in mammals by carrying out the methods described and claimed in the present application. The Office Action fails to provide any basis for doubting the truth or accuracy of any statement in the Declarations. MPEP 2164.04. At most, the Office Action alleges that the Declaration of Dr. Barsoum lacks probative value because it describes "human colon and breast cancer models that were not described in the instant specification." What is the *legal basis* for the Examiner's contention that such assays must be described in the specification? Applicant respectfully submits that nothing in the statute, rules, or case law requires that the specification describe the assays set forth in a Declaration. In the absence of legal support for this requirement, a rejection on this basis must be withdrawn.

The Examiner is also respectfully reminded that the evidence of enablement provided by an applicant "need not be conclusive but merely convincing to one skilled in the art." MPEP 2164.05. The Office Action states that the cancer models described in the Declaration do not "approximate in any way any real world therapeutic application."

This conclusion simply is unsupported in law or science. The disclosed animal models are *art-accepted* models and demonstrate baculovirus-mediated exogenous gene expression in a mammal, as described and claimed in the present application (see, e.g., ¶13 of the Declaration of Dr. Barsoum). The Declaration of Dr. Boyce also relies upon art-accepted animal studies, demonstrating baculovirus-mediated exogenous gene expression in mammals. The Office Action fails to provide any *evidence* to the contrary. MPEP 2164.02.

At most, the Office Action states that the working examples described therein "did not involve *systemic* administration of vectors (especially not to liver)" [emphasis added]. Applicant points out that the claims do not require systemic administration of vectors. Additionally, the Examiner's skepticism as to "gene therapy as a whole" simply does not outweigh Applicant's *specific* demonstration that baculoviruses can be made and used as described and claimed. Having described how to make and use baculoviruses to obtain exogenous gene expression in a mammal, and having demonstrated the successful use of the claimed invention, Applicant has complied with the requirements of 35 U.S.C. §112, ¶1.

The Office Action Fails to Establish that Undue Experimentation Would be Required

Pages 4-5 of the Office Action set forth the Examiner's belief that "gene therapy as a whole" was "unpredictable" as of the filing date of the present application.[1] The

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[1] Applicant notes that the Office Action failed to include form PTO-892 and copies of the cited references as required by MPEP 707.05(a). The Examiner is requested to provide such documents with any subsequent correspondence.

Office Action is deficient because, regardless of the state of "gene therapy as a whole," the Office Action fails to establish that the *claimed* method for using baculoviral vectors to express exogenous genes would require *undue* experimentation. A proper rejection for lack of enablement requires that the Patent Office "back up assertions of its own with acceptable evidence or reasoning which is *inconsistent with [Applicant's] contested statement*. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure" [emphasis added]. MPEP 2164.04, *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971). Despite this requirement, none of the evidence or reasoning presented in the Office Action is inconsistent with Applicant's assertions and evidence that baculoviruses can be used as claimed.

The Office Action states that the specification "does not teach how one skilled in the art is to overcome any of the problems that have plagued gene therapy." Office Action at 5. To the contrary, the specification discloses that baculoviral vectors should be used to express an exogenous gene in a mammal, and the specification provides the necessary guidance with respect to how to achieve such exogenous gene expression. None of the generalizations set forth in the Office Actions refute Applicant's demonstration that the invention can be practiced as claimed by carrying out the methods disclosed in the specification.

The Boyce et al. Publication Does Not Support the Lack of Enablement Rejection

The Boyce et al. publication (*Proc. Natl. Acad. Sci. USA 93*:2348-2352 (1996)) states that "much more work will be necessary to evaluate the safety and efficacy of AcMNPV as a tool for human gene therapy" (emphasis added). This statement does not

support a rejection under 35 U.S.C. §112, ¶1. The recognition of a further need for evaluating the efficacy of AcMNPV as a tool for human gene therapy is not a concession that further work is needed to determine whether the invention as disclosed in the specification is in compliance with the requirements of the patent statute. Indeed, it is well established that the need for further research and development does not prevent compliance with 35 U.S.C. §112, ¶1:

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. [emphasis added.]

In re Brana, 51 F.3d 1560, 1568 (Fed. Cir. 1995). Thus, Dr. Boyce's recognition of the need for further evaluation of the efficacy of AcMNPV as a tool for human gene therapy is entirely consistent with the Federal Circuit's holding that such a need for further research and development is expected while complying with 35 U.S.C. §112, ¶1. Thus, under *Brana*, the Boyce publication does not support the rejection for lack of enablement.

Rejection Under 35 U.S.C. §112, ¶2

Claim 1 was rejected as being indefinite. This rejection has been obviated by the foregoing amendment and by the following remarks. The Office Action states that the specification is "indefinite in its recitation of a method for *introducing into a cell* a baculoviral vector." This rejection has been obviated by the foregoing amendment, specifying that the baculovirus is introduced into a mammal comprising the cell.

The Office Action states that "'[M]aintaining said cell' within the context of [a] mammal does not appear to be subject to the artisan's control." Applicant respectfully points out that the artisan can control how the cell is maintained, e.g., the artisan can allow the cell to live, and thus allow the exogenous gene to be expressed, or the artisan could cause the cell and/or the mammal to die, thereby preventing exogenous gene expression. A person of ordinary skill in the art would readily be able to determine whether the cell was maintained under conditions such that the exogenous gene was expressed. Accordingly, the metes and bounds of the claim are clear, and the rejection under 35 U.S.C. §112, ¶2, should be withdrawn.

Double Patenting

Claim 1 was rejected for alleged obviousness-type double patenting over claim 1 of U.S. Patent No. 5,731, 182. This rejection will be obviated by submission of a Terminal Disclaimer in view of U.S. Patent No. 5,731,182 upon receipt of notice that the claims are otherwise in condition for allowance.

Other Matters

The Office Action states that Reference BB (DE 44 07 859 C1) cited in the Information Disclosure Statement filed "was considered only with respect to the English abstract provided...." Applicant notes the Patent Office's duties under 37 C.F.R. §1.97 and MPEP 609, and respectfully requests that the Examiner initial and return form PTO 1449, indicating that all of the art submitted in the Information Disclosure Statement has been considered in compliance with 37 C.F.R. §1.97 and MPEP 609.

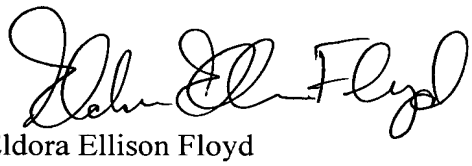
Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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Version with markings to show changes made

1. (Twice Amended) A method of expressing an exogenous gene in a mammalian cell, said method comprising:

a) introducing into [the cell] a mammal comprising said cell a baculovirus the genome of which comprises said exogenous gene[, wherein the baculovirus is introduced by administering the baculovirus to a mammal comprising the cell]; and

b) maintaining said cell under conditions such that said exogenous gene is expressed.

New claims 27-36 have been added.